AKADEMIJA NAUKA I UMJETNOSTI BOSNE I HERCEGOVINE
АКАДЕМИЈА НАУКА И УМЈЕТНОСТИ БОСНЕ И ХЕРЦЕГОВИНЕ
ACADEMY OF SCIENCES AND ARTS OF BOSNIA AND HERZEGOVINA

WORKS

VOLUME XCIV

Department of Medical Sciences
Volume 34

Centre of Medical Research
Volume 4

Editor
Faruk Konjhodžić
correspondent member of the ANUBiH

SARAJEVO 2005

ADVERSE REACTIONS OF CYCLOSPORINE IN PATIENTS AFTER KIDNEY TRANSPLANTATION

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Abstract

Increased level of cyclosporine in whole blood leads to different severe adverse reactions causing disturbance in function of kidney as well as liver, central nervous sistem, increased blood pressure, gingival hipertrophy. Low doses of cyclosporine lead to HVGR (host versus graft reaction).Cyclosporine level in whole blood does not depend upon dose only. So the level of cyclosporine has to be determined regularly to avoid either severe adverse reactions of the drug or HVGR.

In the present study we analysed cyclosporine levels in 15 patients after kidney transplantation. Cyclosporine levels were determined by fluorescence polarization immuno assay, and the monoclonal whole blood was carried out by analizer ABBOT - TDX. In these patients the cyclosporine level determinants were performed six times during three months. In intervals of 15 days, at the exactly same time, we followed the parameters determining the kidney and liver functions : creatinin, ALT(Alanin aminotranssferasis), AST(Aspartat aminotranssferasis), serum concentraratins of bilirubine, and ultrasound diagnostics of kidney and liver). The results of our study have shown that frequent monitoring of cyclosporine concentrations in whole blood in patients with transplanted kidney is extremly important. It is the way how to maintain the cycosporine levels in whole blood in the recommended interval between 100 and 300 ng/ml. By doing it the adverse drug reactions of cyclosporine in our study were reduced to a minimal level.

Key words:Cyclosporine-Determination-Nephrotoxicity-Hapatotoxicity

Introduction

Comparing drug cyclosporine with other older immunosuppressive drugs we noticed survival graft of skin, heart, kidney, bone marrow , lung, and liver was improved (1,2). Cyclosporine affects immune response which is specifficly aimed against transplantation antigen (3). It acts as immunosuppresive suppressing clonal expansion and functinal activation of lymphocities(4,5) The most serious factor that limits its use is cyclosporine toxicity, first of all nephrotoxicity which is dose dependent(6). Cyclosporine applied in high doses is also causes hepatotoxicity (especially in patients with earlier damaged liver function) (7). One of more adverse drug reactions is gingiva hypertrophy, hirsutismus and side effects of CNS (8).

Monitoring of cyclosporine is important indicator during immunosuppressive cyclosporine therapy.Although cyclosporine is very toxic drug the number of adverse drug reactions may be reduced by successive follow up of drug concentration in blood (9)

Material and methods

In our study we determined cyclosporine levels in blood of kidney transplantation patients. The follow up was carried out in Internal Clinic, partly in Central lab University Clinic Center, and partly in the Department of Pharmacology Tuzla University. The cyclosporine level was carried out six times every 15 days. The cyclosporine determination was performed by FPIA using ABBOT-TDX. As a sample EDTA blood was used ,which was first treated with reagent for hemolisis and precipitation. Afterwards cyclosporine was determined in supernatant. Test sensitivity is 25 ng cyclosporine per 1 ml of blood. Statistic treatment of the results was performed by correlation determination.

Results

The cyclosporine level obtained by application of FPIA manhood were between 45 and 1.000 ng/ml blood with average level 182 ng/ml blood.The creatinine level was between 97 and 977 nmol/L average 190 ng/ml blood.Aspartat aminotranssferasis level was between 115 and 889 nkat/l. Average was 318 nkat/L and the level of alanin aminotransferasis was between 110 and 1699 nkat/L with an average of 365 nkat/L:The results can be seen in the tab. 1. Kidney transplant recipient was between 22 and 65 year old and the average was 36 years. Kidney transplant was between 1 and 12 years old and the average was 5.5 years.

Table 1. The concentrations of cyclosporine in whole blood, serum creatinines, serum AST and ALT in patients after kidney transplantation (X-1),and averages (X-2)).

	(X-1)	(X-2)
Cyclosporine(ng/ml)	45-100	182
Creatinine(nmol/L)	97-977	190
AST(n kat/l)	115-318	318
ALT (n kat/l)	110-1699	365

Discussion

Apart from determination of cyclosporine level in blood we also observed parameters relating to kidney and liver function (serum creatinine and transaminases due to high cyclosporine nephrotoxicity and hepatotoxicity (10). Cyclosporine level should be maintained within referent once between 100 and 300 ng/ml of blood in order to prevent graft rejection on one hand and as well as adverse drug reaction on the other hand (11). We observed low cyclosporine level in patients exposed to infection (12). Higher cyclosporine doses should be given immediately after transplantation because bioavialability is gradually increased during the treatment, so oral doses should be gradually reduced to maintain permanent concentration in blood. By performing frequent cyclosporine monitoring we have reduced nephrotoxicity hepatotoxicity to a minimal level ,what justifies the aim of this work (13,14)

There was no statistic significant linear correlation between the concentration of cyclosporine level in blood and the level of serum creatinine, because we tried to maintain the cyclosporine level within the refemce value in successive observation of the drug level in blood.

There was no statistic significant correlation between cyclosporine level in blood and the AST and ALT levels i.e.The correlation coefficient does not different from 0 and therefore we can prevent hepatotoxicity. Frequent cyclosporine monitoring has its significance for future research to reduce adverse drug reactions to a minimal level in applying this drug(15,16,17,18,19). Other significant effects are related to nephrotoxicity and hepatotoxicity effect in particular.

Conclusion

In regard to expressive nephrotoxicity and hepatotoxicity as well as related great number of possible adverse effects during application of cyclosporine teary, it is required to follow up successive drug concentration in blood. We have proven in this work that monitoring of cyclosporine concentration in blood may reflect efficiency immunosuppressive application.

Apstrakt

Povečani nivo ciklosporina u punoj krvi može voditi u vrlo teške i neželjene poremećaje u funkciji bubrega, jetre, centralnog nervnog sistema, povečani krvni pritisak, gingivalnu hipertrofiju.Niske doze ciklosporina vode u HVGR reakciju, domaćina protiv presada.Ciklosporin vrijednost u punoj krvi nije ovisna samo od doze.U našoj studiji mi smo analizirali vrijednosti ciklosporina u 15 pacijenata nakon bubrežne transplantacije.Vrijednost ciklosporina bile su određivane fluroscetnim polarizacijskim imunoesejom a, primjenjen je monoklonalni test u punoj krvi na aparatu ABBOT-TDX.U ovih pacijenata vrijednosti ciklosporina su određivane 6 puta u trajanju od tri mjeseca.U intrevalima od 15 dana normalno u isto vrijeme, mi smo određivali laboratorijske parametre koji determiniraju funkciju bubrega i jetre : kreatinin, AST, ALT, serumsku koncetraciju bilirubina, ultrazvučni pregled bubrega i jetre.Rezultati u ovoj studiji su pokazali da često rađen monitoring ciklosporina u punoj krvi u pacijenata sa presađenim bubrezima je ektremno važan.To je put da se vrijednost ciklosporina u punoj krvi najbolje održava između 100-300 ng/ml.Kod ovih vrijednosti neželjene reakcije od ciklosporina bile su reducirane na minimalni nivo.

Ključne riječi Ciklosporin-određivanje-nefrotoksičnost-hepatotoksičnost

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